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# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

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**INVENTOR(s) / APPLICANT(s)**

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**TITLE OF THE INVENTION (280 characters max)**

SUBSTANCE FOR INCREASING THE PH IN THE STOMACH, SUCH AS ANTACIDS, AND ANTIOXIDANTS WORK SYNERGISTICALLY IN THE STOMACH MEDIUM

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

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25,457
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# SUBSTANCE FOR INCREASING THE PH IN THE STOMACH, SUCH AS ANTACIDS, AND ANTIOXIDANTS WORK SYNERGISTICALLY IN THE STOMACH MEDIUM

Inventors: Niva Shapira and Joseph Kanner

## Introduction

Heartburn is the most common clinical manifestation of gastro esophageal reflux disease (GERD) in human (1).

Approximately 40% of the US population experiences heartburn each month; and up to 7% have it daily. Most people with GERD self-treat the disorder by avoiding foods that seems to aggravate symptoms, life-style alteration and acid suppressors medications such as antacid and acid-suppressor H2-receptor antagonists (2).

The gastric acidity is necessary for food digestion and protection against pathogenic bacteria, however, over acidity is also known as a risk factor for stomach ulceration and stomach esophagus cancer (3).

Oxygen free radicals are implicated in the pathogenous of stress and food induced gastric mucosal injury. Restrain stress, spicy food diet, high-fat diet and ethanol increase $O_2^{\cdot}$, $HO^{\cdot}$, LOOH and DNA fragmentation in gastric mucosal cells (4).

Most recently we published that gastric fluid is an excellent medium for further peroxidation and free radical generation from dietary oxidized foods such as red-meat and heated oil. The results showed that the free lipid radicals co-oxidized vitamins such as ß-carotene and vitamin C. In the presence of catechin or red-wine polyphenols, the catalyzers breakdown hydrperoxides to zero, totally preventing lipid peroxidation and co-oxidation of other compounds. The results indicate the potentially harmful effects of oxidized fats in food in the presence of endogenous catalyzers found in food and the major benefit for included in the meal plant derived antioxidants (5).

Indeed polyphenuols such as quercetin and catechin protects stomach mucosal cells from the injury of ethanol, nitrite, water immersion restraint stress or non-steroidal anti-inflammatory drugs (6,7).

The relationship between vegetable and fruit consumption and rthe risk of cancer results from 206 human epidemiological evidences studies showed for protective effects of high vegetable and fruit consumption against cancers of the stomach, esophagus, oral cavity, pharynx and colon (8).

The aim of this study was to demonstrate that a combination between an antacid and a flavonoid class, work synergistically to prevent in simulated gastric fluid, lipid peroxidation through a radical reaction induced by myoglobin and free iron.

## Materials and Methods

Metmyoglobin (metMb, from horse skeletal muscle), soybean lipoxygenase (type I-B), β-carotene, linoleic acid, Tween 20, butylated hydroxytoluene (BHT), catechin, pepsin (A, from porcine stomach mucosa), ferrous ammonium sulfate. Xylenol orange, and triphenylphosphine (TTP) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Sodium chloride, hydrogen peroxide (30%) and L (+)-ascorbic acid (AA) were obtained from Merch (Darmstadt, Germany). Ferric chloride (Fe) was obtained from Riedel-de-Haen (Hannover, Germany). Soium borohydride was from BDH (poole, NJ, USA). Grilled turky meat (shawarma) were bought at commercial stores in Israel. Human gastric fluid (HGF) was collected with permissiomn from a fasting woman (age 25) during regular gastric endoscopic tests, and kept at -80°C pending use simulated gastric fluid (SGF) was freshly prepared according to the U.S. Pharmacopoeia (9).

## Hydroperoxides measurement in linoleic acid emulsions

Spectroscopic measurements. Hydroperoxides determined by means of the ferrous ion oxidation- xylenol orange (FOX2) method (10), including spectral analysis at 560 nm with $H_2O_2$ standard curve.

Catechin was dissolved in 10% ethanol in water, thus the ethanol concentration in the reaction tubes were incubated in triplicate in a shaking bath at 37°C for 180 min. Samples of 25 or 50 µl were taken from the tubes during the incubation and added to 475 or 950 µl, respectively, of FOX2 reagent. Before each experiment, old stock solution of linoleic acid was mixed with fresh solution in order to maintain an accurately consistent initial level of hydroperoxides.

I had been confirmed in preliminary experiments that the presence of metMb, Fe, AA, wine, or catechin themselves, at the concentrations used, did not interfere with the FOX2 assay.

Hydroperoxides measurement in turkey muscle tissue

The grilled turkey meat, in the form of small slices, was divided into portions and kept at -80°C peding use in the experiment. One part of this muscle tissue was ground with three parts of liquid for 1 min. in a lavoratory blender (Waring, New Hartford, CT, USA) and adjusted to pH 3.0. the liquid contained SGF with red wine, or ethanol solution or water as controls. The wine was diluted with 12% ethanol solution, so that the ethanol content (final concentration 6%) was equal in all of the treatments, except for the water control. The meat –liquid mixture of each treatment was divided among several tubes and incubated in a shaking bath at 37°C for 180 min. At five times points, the hydroperoxides in the samples were extracted by 10-fold dilution in methanol under slow stirring for 15 min, followed by paper filtering (cat. No. 1442, Whatman, England). One hundred microliter samples of the filtered solution were subjected to the FOX2 assay, which included TTP reagent controls, in order to prevent potential interference from ferric ions and the red wine pigments.

Results

Grilled turkey meat, one part of this muscle tissue was ground with three parts of simulated gastric fluid for 30 sec in a laboratory blender and adjusted to pH 3.0.

The heated red turkey meat was found to contain about 180 μM hydroperoxides and malondialdehydes concentration 10-20 times higher than those in the fresh muscle.

In addition to control the heated red turkey muscle was ground in the presene of an Antacid changing the pH to 5.0 and with or without catechin to a concentration of 2.5 mM. The results show a rapid lipid peroxidation in the control samples and after a incubation of 180 min the level of the hydroperoxides rose to more than 1400 μM.

Lipid peroxidation of the sample contained antacid, which change the pH of the gastric fluid to 5.0 decrease lipid peroxidation and the accumulations of hydroperoxides.

However, the sample contained both Antacid and catechin not only inhibited lipid peroxidation, but also reversed the reaction and broke down hydroperoxides to zero concentration.

Discussion

Lipid peroxidation in red muscle tissue is potentially catalyzed by an iron-redox cycle formed by ferrous ions and ascorbic acid. Metmyoglobin, the red pigment could work in muscle tissue as a prooxidant or antioxidant (11, 12). Our data demonstrated that human stomach fluid, having low pH and dissolved oxygen following a meal, is a suitable medium for further lipid peroxidation. The acidic pH of the gastric fluid significantly amplified the peroxidation of lipids catalyzed by dietary endogenous catalysts, found in foods such "free" iron or hemeproteins. These results are in agreement with others which found that the consumption of hydroperoxides and hydrogen peroxide with "free" iron or metmyoglobin is stongly pH dependent (5).

Plant derived polyphenolic antioxidants such as red-wine not only prevented the build up of oxidized products, but also in association with heme-proteins, stimultated the hydroperoxides breakdown and inverted catalysis from pro-oxidation to antioxidation. Several factors affect the displacement of electrons and hydrogen from the phenolic hydroxyl group; they include additional OH or OR groups around benzoid ring and pH. High pH increase the rate of hydrogen displacement from polypheniolic compounds and therefore increase their antioxidant effects (13).

The introduction in the system of antacid and catechin inverted the reaction from prooxidation to antioxidation. Once the concentration of the hydroperoxides drop to zero, the system remains stable against pro-oxidative effects for long time (Figure 1).

The synergistic effect of antacid on the activity of the catalyzers and antioxidant was achived because by increasing the pH the prooxidative effects drop and the catechin antioxidative activity rose two effects which work to increase the antioxidative tone of the system.

The antiulcerogenic and anti-oxidant effects of verious flavonoids have been frequently reported (6,7). More over, catechin was found to significantly inhibited the release of gastrin, somatin and histamine (7).

We believe that a combination between an antiacid and a polyphenol antioxidant such catechin, quercetin or other polyphenols could be used as a therapeotic digestive additive before meal to prevent and suppress gastric mucosa lesions in human.

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Appendix 1

Synergistic composition of Antacids and Antioxidants

The new concept in treatment of over acidity

Abstract:Antacids market, The Incidence

1) clinical conditions treated by Antacids

1a) Heartburn:

1b) Stomach ulcer

1c) GERD-

1d) Gastro- esophagal cancer-

The cost of the disorder:

2) The Antacids:

Definitions: Functions, Usage, Adverse effects:

2b) Indications

Contraindications:

2c) Examples of antacid families:

Natural Antacids : Gastro-AD, Prelief Tamer combination

2d) Brand Names :

2e) Administration and Dosage:

2e1) Differential effectiveness

2f)Antacids Vs surgery for severe heartburn:

3) The Side effects of antacids:

3a)Promoting cancer causing Bacteria:

3b)Powerful antacids might increase cancer risks

Inflammatory response:

Inter- drugs antacids effects:

4) The oxidative component in gastro-intestinal damage;

Reactive oxygen species (ROS)

4a)The oxidative damage in gastric ulceration: Helicobacter pylori-induced oxidative stress and DNA damage in a primary culture of human gastric mucosal cells
The new- antioxidative paradigm
4b) Antioxidant protection starts in the lumen:
4b1)Gastroprotective effects of quercetin.
4b2)Antocyanosides against Inflammation and Ulcer,
4c) Tea Polyphenols May Reduce Risk
4d)Gastric cytoprotection by medicinal plants antioxidants
4e) Antisecretory and antiulcer activities of phyto-antioxidants
4e1)Inhibition of gastric acid secretion by the extracts of Stachytarpheta cayennensis.
4e2) Inhibition of gastric H+, K(+)-ATPase by flavonoids:
4f) In vitro anti-Helicobacter pylori activity of some flavonoids and their metabolites.
4g) Distribution pattern of flavonoids in the gastrointestinal
5) Further protective effect of antioxidants
5a) Gastroprotective agents for the prevention of NSAID-induced gastropathy.
5b) Inhibition of nitrous acid-dependent tyrosine nitration and DNA base deamination by flavonoids and other phenolic compounds.
6)Epidemiological evidence for antioxidants protection
6a) Epidemiological corelation between intake of specific carotenoids and flavonoids and the risk of gastric cancer in Spain.

<u>The problem</u>

Abstract: The gastric acidity is necessary for digestion, protection against pathogenic bacteria, stimulation peristaltic movement and further functions of the stomach and digestive system. However, over acidity is a known associated risk factor for digestion, inflammation, ulceration and cancer of the stomach and the esophagus. Un-protective epithelial cells further contribute to the ulceration process and resulting symptoms and risks.

The answer: The use of Antacids contribute to immediate relief of the over acidity sensation. The limitations of the answer however, researches showed that the duration of the effect is limited- averaged between 60-80minutes and the effectiveness of the various preparations might be limited, sometimes only relieve the acidity in the lower esophagus, where the lining tissues are more sensitive, and not at all in the stomach. This could result in Acidity "rebound" intensive use of antacids.

Un-wanted side effects, i.e. to indigestion, increased risk to inbalanced gastric flora (increased Helicobacter Pylori), inflammation, and cancer of the stomach and esophagus.

The ineffectiveness of other approaches, 10 years evaluation showed that surgery for treating severe heartburn was not found significantly more effective than antacid in the long run.

Recent research findings showed that stomach acidity facilitates oxidative stress and formation of free radicals, which are known contributors to inflammation, ulceration and carcinogenic processes.

The New approach:

The above suggest a rational for combining Antioxidants with Antacids.

Among the Antioxidants, the more relevant ones will be those that are more stable in acid conditions, as they don't turn themselves to proxidants, i.e. phenolic compounds like Flavonoids.

Potential Antioxidants and Flavonoids: Recently, Some Flavonoids found to have significant potential for stomach protection against over-acidity by their contribution to prevent nitrosation, reduced acid secretion, increasing the mucus' layer and protecting the stomach epithelial cells, and more.

The new synergistic composition: The combination between Antacids and Antioxidants, Flavonoids as an example, suggest a Synergistic composition for protection against oxidative damage. Firstly for Gastric & Esophagus Protection where over acidity (and/or responsive over alkalinity ) and chain reaction of free radicals' formation might be mutually self-facilitating. Same composition also effective for protection of oxidizable materials i.e. Antioxidants supplements, Medicines, Antibiotics, Hormones and/or every food or orally taken material. Firstly for human but also for animals like Turkey and Horses, that are assumed to be most benefited by this procedure.

The advantage of the synergistic composition:The synergistic composition of Antacids and Antioxidants can contribute to: 1)Reduce the use of Antacid 2) Reduce the unwanted side effects and 3)Increase the effectiveness of the antacids'protection against risks factors to the stomach and the esophagus.

Due to the 'Chain-Reaction' nature of the process, minimal amounts of both Antacids and Antioxidants could at the initial stage already stop the reaction and thus increases

the synergistic effectiveness of the combination beyond the separate effects of either of them, is related to timely and physiology synergism especially if given at later stages. The synchronicity between the acidity sensation and the real physiological process of internal damaging to the epithelial cells help attaining the right timing for high efficacy of the combination.

Background

Antacids market: Antacids market was at 1997 69.1 million$.

The acidic risk

The Incidence: Approximately 40% of the us population, about 106 million people, experience heartburn at least once a month, and up to 7% have it daily. Heartburn is the most common clinical manifestation of gastro esophageal reflux disease (GERD) in human (I). Most people with GERD self-treat the disorder by avoiding foods that seems to aggravate symptoms, life-sty le alteration and acid suppressors medications such as antacid and acid-suppressor H2-receptor antagonists (2).

The physiology:The gastric acidity is necessary for food digestion and protection against pathogenic bacteria, however, over acidity is also known as a risk factor for stomach ulceration and stomach esophagus cancer (3).

1) clinical conditions treated by Antacids

1a) Heartburn: Heartburn-described as the telltale burning in the middle of chest after a meal or when reclining, and some may complain of regurgitation, especially when lifting or bending over after meals and after they go asleep. ,is a common conditio. The cause of pain is stomach acid - the acid that helps to digest the food washes back up into the esophagus. Normally when you eat, food travels from your mouth down the esophagus through a one-way valve called the lower esophageal sphincter (LES). The LES is the opening to your stomach. It normally opens only when you swallow, allowing food to enter the stomach, and then closes quickly.

If there's too much acid, or if the LES doesn't work properly, food and stomach acid can wash back up (reflux) into the esophagus. The reflux irritates the lining of the esophagus and causes heartburn. If the muscles in the stomach don't keep food and acid moving down the digestive tract, the heartburn can worsen

1b) Stomach ulcer : A stomach gastric ulcer is a raw area or open sore that develops in the lining of the stomach. The stomach's lining has a protective layer of cells that produce mucus. The mucus prevents the stomach from being injured by stomach acids and digestive juices. When this protective layer is damaged, an ulcer may occur.

1c) GERD: Gastroesophageal reflux disease (GERD) not only is unpleasant, but also can put a patient at risk for Barrett's esophagus or adenocarcinoma of the esophagus. Heartburn is the most common clinical manifestation of GERD. For most people, GERD is more of a nuisance than a threat, because the majority of patients do not ulcerate their esophagus with the subsequent risk of bleeding or stricture formation, nor do they develop upper-airway problems, such as asthma, aspiration pneumonia, or chronic cough. Only 5% to 10% of patients with complaints of reflux have demonstrable endoscopic esophagitis.

High sensitivity of Esophageal epithelial cells :There is apparent need for greater suppression of gastric acid secretion to control acid-peptic injury to esophagus as opposed to that of stomach and duodenum. Among the differences cited that may account for the reduced acid-resistance of the esophageal epithelium are: 1) a lack of mucus and bicarbonate secretion by surface epithelial cells, 2) a lack of defensive enhancement by prostaglandin release, 3) a lack of an effective mucus cap after injury, and 4) an apparent lack of capacity to rapidly heal erosions by the process of epithelial restitution (Orlando RC, 1996).

1d) Gastro- esophagal cancer- Acidity as predictor: People who suffer from chronic heartburn and acid reflux are substantially more likely to develop a deadly cancer of the esophagus. Swedish researchers found that people who suffered heartburn, regurgitation or both, at least once a week, had eight times the risk of developing adenocarcinoma, the most deadly form of esophageal cancer. The risk was 11 times higher for those who suffered from acid reflux at night. Interestingly,there was no increased risk for another form of esophageal cancer called squamous-cell carcinoma. It is assumed that because the esophagus isn't lined like the stomach, stomach acid irritates the lower esophagus and, over time, triggers precancerous changes that can progress into cancer.

However, Researchers also found that people who take antacids and other medications to battle heartburn and acid reflux do not reduce their cancer risk.

Whereas the overall risk for esophageal cancer is still very low (about 12,500 /year compared to 20 to 30% Americans reporting heartburn at least once monthly), it grows among white men. A complication of GERD called Barrett esophagus is a strong risk factor for esophageal cancer.

Incidence: 0.4 percent per year, compared to 0.07 percent in those without Barrett esophagus.

The cost of the disorder:

Direct costs include visits to physicians' offices, inpatient, outpatient and emergency visits to hospitals, as well as the costs of prescription and OTC medications. Indirect costs measure the cost of time away from work. Overall, GERD is the most expensive in total cost with $10 billion each year.

Popular OTC and pharmaceutical solutions to problems caused by excessive digestive acid include Pepcid AC, Tums, Zantac, Maalox, Prilosec, and Mylanta. And their parent pharmaceutical companies spend lots of money promoting them. According to The Tan Sheet (June 18, 2001), direct-to-consumer spending for Prilosec in 2000 amounted to $107.5 million - a 34 percent increase from the prior year. In comparison, the combined spending for Pepcid AC, Tums and Zantac 75 amounted to $93.4 million.

2) The Antacids answer:

Definitions:They are mainly alkaline drugs, that are administered orally and the cation of the antacids binds with the chloride of the HCl in the stomach to form a salt. They raise the gastric Ph to above 4.0. The duration of action of soluble antacids is usually longer than that of insoluble antacids. Functions: The effect of antacids on the stomach is due to partial neutralisation of gastric hydrochloric acid and inhibition of the proteolytic enzyme, pepsin. Each cation salt has its own pharmacological characteristics that are important for determination of which product can be used for certain indications.

Indications: Antacids are taken orally to relieve heartburn, hyperacidity and acid indigestion, for pain of peptic ulcer and for reflux esophagitis. They work by neutralizing excess stomach acid. Many mild cases of heartburn respond well to

medications, which help to absorb excess stomach acids and increase the rate of digestion. Liquid antacids most often work faster and neutralize stomach more quickly than their pill or tablet alternatives. Antacids have been used for duodenal and gastric ulcers, stress gastritis, gastro-oesophageal reflux disease, pancreatic insufficiency, non-ulcer dyspepsia, bile acid mediated diarrhoea, biliary reflux, constipation, osteoporosis, urinary alkalinisation and chronic renal failure as a dietary phosphate binder. The development of histamine H2-receptor antagonists and proton pump inhibitors has significantly reduced usage for duodenal and gastric ulcers and gastro-oesophageal reflux disease. However, antacids can still be useful for stress gastritis and non-ulcer dyspepsia. Antacids are likely to continue to be used for non-ulcer dyspepsia, minor episodes of heartburn (gastro-oesophageal reflux disease) and other clear indications

Contraindications:

Most adverse effects from antacids are minor with periodic use of small amounts. However, when large doses are taken for long periods of time, significant adverse effects may occur. ( Antacids revisited:a review of their clinical pharmacology and recommended therapeutic use.Maton PN and Burton ME, Drugs 1999,57(6):855-70). Antacid drug interactions are well noted, but can be avoided by rescheduling medication administration times. This can be inconvenient and discourage compliance with other medications.

Antacids may also be given in combination with simethicone, which may relieve the symptoms of flatulence, and also to treat stomach or duodenal ulcers. With larger doses magnesium hydroxide (magnesia) and magnesium oxide antacids produce a laxative effect. Some antacids, eg. Aluminum carbonate and aluminum hydroxide, are used with a low-phosphate diet to treat hyperphosphatemia, and can also be used with a low-phosphate diet to prevent the formation of renal calculi.

2c) Examples of antacid families:

- Aluminum hydroxide - non-systemic, weak, raises pH of stomach 4-5
  Delays gastric emptying rate, May cause constipation, like all antacids, causes "acid rebound"
- Calcium carbonate (Tums) - non-systemic, raises pH to 7.0, increases gastric emptying. May cause more "acid rebound" than others,

- Magnesium hydroxide - non-systemic, used as an antacid and cathartic, raises pH of stomach contents to 9, increases gastric emptying rate. Should not be taken by person with renal difficulties.
- Sodium bicarbonate (Alka Seltzer) - systemic, most potent antacid, increases gastric emptying rate. Contraindicated in hypertensives, Potential for drug interaction high due to its effect on urine pH

Natural Antacids:

The natural products industry has several strong acid-fighters to neutralize the acid on the food or in the beverage before ingesting. Gastro-AD, which is produced from the fermentation of soy by a specific probiotic strain, Lactobacillus delbrueckii. Prelief calcium glycerophosphate is used to take acid out of acidic foods and beverages for more comfortable consumption, tablets to be swallowed with the first bite or drink of the bothersome food/beverage, while the granulate is added to the serving prior to consumption.

Tamer combination of the same natural actives - calcium carbonate, potassium and magnesium hydroxide are many times more potent- 11 times more than Tums, 16 times more than Maalox, and 3 times more than Mylanta - without many nutritional negatives like aluminum, sodium, gelatin, etc."

2d) Brand Names : Antacid combinations :Acidin( east india), Aciguard (Knoll), Alcaine MPS ( sun pharma) Algiflux ( Panacea), Almagel ( IDPL) Alucinol (Franco Indian ) Centadid ( Centaur) Digene gel ( Knoll pharma ) Disogel (Concept), Gelusil (Parke Davis), Mucaine (wyeth lederle )

2e) Administration and Dosage:It is given orally as gel, tablets or syrup . Aluminium Hydroxide tab 0.84 gm ; suspension 0.6g/10ml give sixth to eighth hourly. Magnesium Hydroxide suspension ; 0.4 gm / 5 ml given every 6 to 8 hrs.

2e1) Differential effectiveness :In the oesophagus:Both Mg/Al and Calcium antacid formulations significantly increased esophageal pH, as compared with placebo. Onset of action was faster with the Al(OH)3/Mg(OH)2 formulation than with the CaCO3 in 41 subjects, slower in 13 subjects, and identical in 29 subjects. Area under the esophageal pH--time curves after dosing were significantly greater for Al(OH)3/Mg(OH)2 than for CaCO3 ($p < 0.05$) and significantly greater for CaCO3

than for placebo ($p < 0.05$). The duration of Al(OH)3/Mg(OH)2 action in the esophagus was 82 min and 60 min for CaCO3 ($p < 0.05$). In the stomach, only Al(OH)3/Mg(OH)2 increased gastric pH compared with placebo. Moreover,after ingestion of calcium carbonate, gastric pH usually remained at or below placebo values, a finding consistent with a calcium carbonate-induced "acid rebound." The duration of Al(OH)3/Mg(OH)2 action in the stomach was 26 min. These findings demonstrate the efficacy and relative superiority of the particular tested aluminum/magnesium hydroxide formulation compared with the calcium carbonate preparation at increasing esophageal and gastric pH. However, the magnitude and duration of action of both antacids on esophageal pH, in contrast to minimal effects on gastric pH, suggest strongly that the lower esophagus is the primary site of antacid activity in relief of heartburn (Decktor DL,1995).

3) The Side effects of antacids:

3a)Promoting cancer causing Bacteria: A new report shows that taking antacids for heartburn may promote the growth of ulcer bacteria Helicobacter pylori , that also cause cancer. Scientists think the lower acidity produced by the antacid may promote the growth of the bacteria. Testing the strongest antacids on the marke (Prilosec, Losec and Prevacid), all within the proton pump inhibitor family showed that they were the most dangerous to use for long periods of time.

3b)Powerful antacids might increase cancer risks The gastrin hormone in the stomach stimulates the production of gastric acid. Certain conditions that increase the gastrin hormone in the stomach can also increase the risk of stomach cancer( Gunnar Qvigstad's). Previous research has shown that strong acid-reducing medication increases the level of gastrin in the stomach'.

Inflammatory response: Mice treated with antacids drugs for a two-week period developed stomach inflammation, which was caused by overproduction of bacteria, that subsided when the mice were given antibiotics. While the researchers concluded that using these drugs was safe for the short-term, patients suffering from extensive indigestion should consider anti-inflammatory drugs instead.

Inter- drugs effects: Fluoroquinolones : Antacids may reduce the potency of this drug. Cellulose sodium phosphate : Calcium-containing antacids may reduce the potency of cellulose sodium phosphate; with magnesium-containing antacids may prevent either drug from acting effectively; antacids should not be taken within 1 hour

of cellulose sodium phosphate. Isoniazid (oral) : Aluminum-containing antacids may reduce effects of isoniazid; isoniazid should be taken at least 1 hour before or after the antacid. Ketoconazole, methenamine : Antacids may decrease the effects of ketoconazole or methenamine; these drugs should be taken 3 hours before the antacid. Mecamylamine ; Antacids may potentiate the effects of mecamylamine, Sodium polystyrene sulfonate resin (SPSR) : may decrease the effectiveness of antacids. Tetracyclines (oral) : may decrease the effects of both drugs; antacids should not be taken within 3 to 4 hours of tetracyclines.

Antacids effectiveness Vs surgery for severe heartburn: In a follow-up on patients to determine whether those who had surgery for the disease fared better than those who took prescription medication found,surprisingly, that two-thirds of the surgery patients still took anti-reflux medication regularly. The two group had similar esophageal stictures (narrowing from scarring) and cancer.

4) The oxidative component in gastro-intestinal damage;

Restraint stress, spicy food diet, high-fat diet and ethanol increased superoxide anion production by 10.0-, 4.3-, 5.7- and 4.8-fold, respectively, in the gastric mucosa, increased hydroxyl radical production by ca. 14.3-, 4.5-, 3.5- and 4.8-fold, respectively, increased lipid peroxidation by 3.6-, 2.4-, 2.6- and 2.0-fold, respectively, increased membrane microviscosity by 11.6-, 6.1-, 7.3- and 5.4-fold, respectively and approximately 4.0-, 2.0-, 2.4- and 2.0-fold increases in DNA fragmentation. In another research, induction of ROS and DNA damage in Gastric Mucosal Cells (GC) following exposure to ethanol (15%), HCl (150 mM) and NaOH (150 mM) were assessed by cytochrome c reduction (superoxide anion production), HPLC detection for enhanced production of hydroxyl radicals, changes in intracellular oxidized states by laser scanning confocal microscopy, and DNA damage by quantitating DNA fragmentation, Incubation of GC with ethanol, HCI, and NaOH increased superoxide anion production by approximately 8.0-, 6.1-and 7.1-fold and increased hydroxyl radical production by 13.3-, 9.6-, and 8.9-fold, respectively, compared to the untreated gastric cell, increased DNA fragmentation by approximately 6.7-, 4.3-, and 4.8-fold, approximately 20.3-, 17.5-, and 13.1-fold increases in fluorescence intensities,demonstrating dramatic changes in the intracellular oxidized states of GC following exposure to these necrotizing agents ( Mechanism of gastroprotection by

bismuth subsalicylate against chemically induced oxidative stress in cultured human gastric mucosal cells. Bagchi D et al D.S.Dis Sci 1999 Dec:44(12):2419-28).Excellent correlations existed between the production of reactive oxygen species and the tissue damaging effects in both gastric and intestinal mucosa. The results demonstrate that physical and chemical stressors can induce gastrointestinal oxidative stress and mucosal injury through enhanced production of reactive oxygen species.

4a) Gastric Antioxidative-protection mechanism: Recently a report, for the first time showed the critical role of an endogenous peroxidase, a major H(2)O(2) metabolizing enzyme, in controlling oxidative damage in gastric mucosa (Bhattacharjee M, 2002). Human gastric mucosa contains a highly active peroxidase in addition to the myeloperoxidase contributed by neutrophil. When myeloperoxidase level increases due to neutrophil accumulation, gastric peroxidase (GPO) level decreases significantly. This leads to further accumulation of endogenous H(2)O(2) that can cause more oxidative damage and aggravate the ulcer. Also mucosal total superoxide dismutase (Mn and Cu-Zn SOD) level decreases significantly under-accumulation of reactive oxygen metabolites (ROM), leading to increased accumulation of O(2)(*-). Gastric ulcer is associated with oxidative damage of the mucosa as evidenced by significant increase in lipid peroxidation, protein oxidation, and thiol depletion indicating accumulation of ROM.

Helicobacter pylori-induced oxidative stress (Dig Dis Sci 2002 Jun;47(6):1405-12).

Helicobacter pylori has been identified in the pathogenesis of chronic active gastritis and peptic ulcer disease and is epidemiologically linked to gastric cancer and lymphoma. Previous studies have demonstrated enhanced production of reactive oxygen species (ROS) in cultured gastric adenocarcinoma cells (ATCC CRL/1739) in association with H. pylori: Approximately 3.5- and 7.7-fold increases in hydroxyl radical ,3.6- and 4.5-fold increases in DNA fragmentation in gastric mucosal cells following incubation with 1:0.5 and 1:1 ratios of H. pylori, respectively. The cytotoxin 87-kDa rich-H. pylori strain 60190 induced greater production of ROS and DNA fragmentation in mucosal cells as compared to the supernatant preparation from

H. pylori strain 60190-v1, in which the cytotoxin gene has been disrupted. This study demonstrates that H. pylori damage is related to the cytotoxine induced ROS.

4b) Antioxidant protection starts in the lumen: In considering the biological importance of dietary antioxidants, attention has usually focused on those that are absorbed through the gastrointestinal tract into the rest of the body. Recent paper raises the argument that the high levels of antioxidants present in certain foods (fruits, vegetables, grains) and beverages (e.g. green tea) play an important role in protecting the gastrointestinal tract itself from oxidative damage, and in delaying the development of stomach, colon and rectal cancer. Carotenoids and flavonoids do not seem to be as well absorbed as vitamins C and E. Hence their concentrations can be much higher in the lumen of the GI tract than are ever achieved in plasma or other body tissues, making an antioxidant action in the GI tract more likely. Additional protective mechanisms of these dietary constituents (e.g. effects on intercellular communication, apoptosis, cyclooxygenases and telomerase) may also be important (Halliwell B, 2001).

4b1)Gastroprotective effects of flavonoids:i.e quercetin

Quercetin is a naturally occurring bioflavonoid with strong antioxidant ctivity. The antioxidant activity of quercetin protects the gastrointestinal tract in several ways. First, quercetin prevents oxidation of lipids. The gastrointestinal tract has an increased exposure to oxidative stress due in part to the lowered pH. It is important to protect the lipid bilayer of the cell wall of the gastrointestinal tract because these cells serve as an important part of the body's immune system. Secondly, quercetin prevents the depletion of glutathione from the cells of the intestinal tract. Glutathione is a cosubstrate for antioxidant enzymes glutathione peroxidase and glutathione reductase. By preserving the level of glutathione, quercetin protects metabolic activity and cellular structure of the highly vulnerable cells of gastrointestinal tract from toxic free radical damage. Vitamin C synergistically improves the ability of the quercetin to preserve glutathione. Thirdly, quercetin increases mucus secretion from gastric cells. The mucus polysaccharide provides a protective buffer for the gastric cells from the low pH of the stomach contents. The reduced contact provides protection from gastric lesions. Quercetin provides an antispasmodic activity that prevents the uncontrolled peristaltic activity found in

diarrhea. The reduced excretion of the intestinal contents provides benefit to the gastrointestinal tract by preventing the constant production of cellular protective materials. Quercetin also reduces the immune response to allergens.

Quercetin inhibits the IgE-mediated allergic mediator release from mast cells as well as IgG-mediated histamine release. Quercetin is a potent inhibitor of the lipoxygenase that metabolizes arachidonic acid, which is the first step towards proinflammatory arachidonic acid metabolites. Thus, quercetin with the assistance of vitamin C in the gastrointestinal tract helps protect against gastric lesions that permit highly antigenic proteins, antigenic compounds and/or infective agents from passing into the body. In addition it prevents the release of components of the allergic inflammation response. Thiobarbituric acid , an index of lipid peroxidation, were increased by ethanol injury, but the increase was inhibited by the administration of 200 mg/kg of quercetin. This dose also induced a significant enhancement in the levels of mucosal non-protein SH compounds (important anti-oxidant agents) and in glutathione peroxidase activity. Exposure of the gastric mucosa to 50% ethanol induced a significant increase in myeloperoxidase activity, an index of neutrophil infiltration. The results suggest that the anti-ulcer activity of quercetin in this experimental model could be partly explained by the inhibition of lipid peroxidation, through decrease of reactive oxygen metabolites (Martin MJ, 1998).

4b2)Antocyanosides against Inflammation and ulcer

Animal studies show that administration of a Bilberry anthocyanoside extract can reduce inflammation.[1] Italian research indicates that Bilberry may also reduce platelet aggregation[2], probably due to increased release of prostacyclin - which has potent blood vessel dilating and platelet anti-agregatory activities.[3]

Oral administration of bilberry anthocyanosides to rats exerted a significant preventive and curative anti-ulcer activity in various experimental models of gastric ulcer without affecting gastric secretion. This activity can be attributed, at least partly, to an increase in gastric mucus.[4]

4c) Tea Polyphenols May Reduce cancer Risk The of Stomach, Esophagus Cancers
Tea-drinkers in a study conducted in Shanghai, China, beginning in 1986, 18,244 men ages 45 to 64 , were about half as likely to develop cancer of the stomach or esophagus as low tea drinkers. This study provides direct evidence that tea polyphenols may act as chemopreventive agents against gastric and esophageal cancer development (Mimi C. Yu, 2002).
Green tea contains the most catechins, followed by oolong and black teas.
Former research formed that catechins have been shown to halt tumor cell growth as well as to protect healthy cells from damage.

4d)Gastric cytoprotection by medicinal plants antioxidants
Preliminary results suggest, that majority of the plants phytochemicals Cytoprotective activity on ethanol-induced ulcer formation( in rat) that is comparable to atropine. The analysis of the chemical constituents of the extracts studied showed the presence of tanins, saponins, flavonoids and coumarins (Gonzales E, 2000).

4e) Antisecretory and antiulcer activities of phyto-antioxidants Inhibition of gastric acid secretion by plant extracts of Stachytarpheta cayennensis.
An ethanolic extract of a plant Bidens pilosa var. radiata Schult. Bip that is used in folk medicine to treat stomach disorders including peptic Ulcers (0.5-2 g/kg), foun to decrease the gastric juice volume, acid secretion, as well as pepsin secretion in pylorus ligated rats. In contrast, ranitidine (50 mg/kg) failed to reduce these lesions. These results indicate that the cytoprotective effect associated with its gastric antisecretory activity that could be due, partly at least, to the presence of flavonoids of which quercetin was identified by HPLC(Alvarez A, 1999).
The most purified active fraction obtained presented a specific activity 5-10 times higher than that detected in the original extract indicated that the antiulcer activity of S. cayennensis is related to a specific inhibition of gastric acid secretion. Cholinergic and histaminergic stimulation of acid secretion were similarly reduced by the extracts suggesting inhibition of common steps in both pathways, possibly at the level of histamine release/H2 receptor interaction, or at the proton pump (Vela SM, 1997).

4e2) Inhibition of gastric H+, K(+)-ATPase by flavonoids: a structure-activity study.
Gastric H+, K(+)-ATPase plays a pivotal role in the final step of gastric acid secretion and some flavonoids, were found to be inhibitors of this enzyme.
The inhibitory potency of flavonoids depends on the number of hydroxyl groups up to four per molecule. The hydroxylation pattern is an important determinant of inhibitory potency, where two adjacent hydroxyl groups (catechol-type), three adjacent hydroxyl groups (pyrogallol-type) or hydroxyl groups at C-3, C-5 and C-7 are a minimum requirement for high potency inhibition; (3) Protection of the hydroxyl group(s) by glycosylation or methylation decreases potency; (4) Saturation of the C-2-C-3 double bond results in a decrease in potency (Murakami S, 1999).

4f) In vitro anti-Helicobacter pylori activity of some flavonoids and their metabolites.
Ponciretin, hesperetin, naringenin and diosmetin were active against HP. Among them, ponciretin was the most potent and its MIC was 10-20 micrograms/ml. Interestingly, these active compounds against HP did nearly not inhibit the urease activity of HP (Bae EA, 1999).

4g) Distribution pattern of flavonoids in the gastrointestinal lumen and wall
Spreading of the flavonoids was accompanied by partial deglycosylation that began already in the stomach where at first quercetin and later apigenin, chrysoeriol and isorhamnetin aglycones were detected
(Pforte H, 1999).
Advantage of antioxidants on antacids in reflux oesophagitis
The new- antioxidative paradigm in gastric protection
Researchers, from Korea, assume that damage from free radicals - could be more important. Preliminary experiments with rats have shown wormwood, which has antioxidant properties successfully treated reflux oesophagitis.
Surgically induced reflux oesophagitis in 60 rats, 15 control 15 were given ranitidine (a common acid suppressant antisecretory) , others were given 30mg or 100mg per kg of the herbal extract. Evaluation of healing 36 hours after surgery, showed that controls
had the most damage (80% ulceration), on acid suppressant (60% ulceration, whreas the antioxidant treated groups appeared to have less severe blistering, lower levels of

inflammation and more extensive healing. The "wormwood" rats also appeared to have more chemicals that protect cells from damage and fewer of the harmful chemicals produced by free radicals. Writing in the journal Gut, the researchers said: "The combination of antioxidant and antisecretory medications is the treatment of choice in the prevention and treatment of reflux oesophagitis."
Still "Rats are not people, and the mechanism by which reflux was caused in these experiments was quite different from those thought to be important in humans, the results cannot therefore be extrapolated directly to treatment of the human disease."
Maybe this prevent our patent?
They suggest that these findings needed to be replicated in humans before people started taking wormwood for the condition.

The mechanism of Bismuth subsalicylate(BSS) protection: The protective ability of bismuth subsalicylate (BSS) was assessed at concentrations of 25, 50, and 100 mg/liter. Incubation of GC with ethanol, HCl, and NaOH increased superoxide anion production by approximately 8.0-, 6.1-and 7.1-fold and increased hydroxyl radical production by 13.3-, 9.6-, and 8.9-fold, respectively,
Administration of BSS decreased restraint stress, spicy food diet, high-fat diet and ethanol-induced gastric mucosal lipid peroxidation by 26%, 36%, 45% and 18%respectively.As BSS acts by scavenging reactive oxygen species suggest that free radical scavenging can be effective in this regard. The present study demonstrates that ethanol, HCl, and NaOH induce oxidative stress and DNA damage in GC and that BSS can significantly attenuate gastric injury by scavenging these ROS.

Mechanism of gastroprotection by bismuth subsalicylate against chemically induced oxidative stress in cultured human gastric mucosal cells(Dig Dis Sci 1999 Dec;44(12):2419-28).

5) Further protective effect of antioxidants

5a) Gastroprotective agents for the prevention of NSAID-induced gastropathy.
Over 30 million people in the world take non-steroidal anti-inflammatory drugs (NSAID's). A large percentage of these individuals will develop gastric ulcers and related complications, a condition known as "NSAID gastropathy". NSAID

gastropathy differs from classic peptic ulcer disease in many ways, and traditional peptic ulcer therapy is largely ineffective in preventing NSAID-induced gastropathy. The prostaglandin misoprostol has been shown to be effective and is approved for the prevention of NSAID gastropathy. NSAIDS cause gastric ulceration in horses:Common NSAIDs include phenylbutazone ('bute') and flunixin meglumine (Banamine™). They act by interrupting the production of prostaglandins. One particular prostaglandin, called PgE2, plays an important role in preventing gastric ulceration. PgE2 does this by decreasing gastric acid production as well as by increasing blood flow to the gastric epithelium. The results are - the horse's stomach becomes more acidic, and this contributes to the development of gastric ulceration.

Many types of structures (flavonoids, peptides, terpenoids, xanthines, others), as well as compounds displaying certain pharmacological actions (5-hydroxytryptamine receptor binding, adrenergic receptor binding, mast cell stabilization, others) have been linked in some way to gastroprotection (Ares IJ, 1998).

5b) Inhibition of nitrous acid-dependent tyrosine nitration and DNA base deamination by flavonoids and other phenolic compounds.

A range of plant phenolic constituents to prevent damage mediated by acidic nitrite was also examined in comparison with the activity of vitamin C. The epicatechin/gallate family of flavonols, constituents of green tea, red wine, etc., demonstrates the most extensive inhibitory properties against both tyrosine nitration and base deamination.

The results also show that ascorbic acid is a poor inhibitor of nitration or deamination under acidic conditions such as those of the stomach. The ability of plant phenolics to scavenge reactive nitrogen species derived from acidic nitrite may contribute to the protective effects of tea polyphenols against gastric cancer (Oldreive C, 1998).

6)Epidemiological evidence for antioxidants protection

6a) Gastric protective carotenoids and flavonoids (spain) Case-control study in Spain, on 354 cases of gastric cancer and 354 controls, support the hypothesis that the well-established protective effect of fruit and vegetables against gastric cancer could, in part, be due to the presence of flavonoids. The adjusted OR of gastric cancer for the highest quartile of total flavonoid intake versus the lowest quartile was 0.44.

Kaempferol intake was found to be protective (OR = 0.48; CI = 0.26-0.88; P for trend = 0.04) comparing the highest versus the lowest quartile of intake. A trend toward lower risk of stomach cancer with higher intake of quercetin was also found (Garcia-Closas R,1999).

6b)Vegetables, fruit, and cancer prevention.

A review of the scientific literature on the relationship between vegetable and fruit consumption and risk of cancer, resulted from 206 human epidemiologic studies and 22 animal studies showed evidence for a protective effect of greater vegetable and fruit consumption against cancers of the stomach, esophagus, lung as well as oral cavity and pharynx, endometrium, pancreas, and colon. Substances present in vegetables and fruit that may help protect against cancer, and their mechanisms, are also briefly reviewed; these include dithiolthiones, isothiocyanates, indole-3-carbinol, allium compounds, isoflavones, protease inhibitors, saponins, phytosterols, inositol hexaphosphate, vitamin C, D-limonene, lutein, folic acid, beta carotene, lycopene selenium, vitamin E, flavonoids, and dietary fiber (Steinmetz KA, 1996).

Antacids and Antioxidants work Synergistically in the Stomach Medium

The aim of this study was to demonstrate that a combination between an antacid and a flavonoid class, work synergistically to prevent in simulated gastric fluid, lipid peroxidation through a radical reaction induced by myoglobin and free iron.

Materials and Methods

Metmyoglobin (metMb, from horse skeletal muscle), soybean lipoxygenase (type I-B), β-carotene, linoleic acid, Tween 20, butylated hydroxytoluene (BHT), catechin, pepsin (A, from porcine stomach mucosa), ferrous ammonium sulfate. Xylenol orange, and triphenylphosphine (TTP) were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Sodium chloride, hydrogen peroxide (30%) and L (+)-ascorbic acid (AA) were obtained from Merch (Darmstadt, Germany). Ferric chloride (Fe) was obtained from Riedel-de-Haen (Hannover, Germany). Soium borohydride was from BDH (poole, NJ, USA). Grilled turky meat (shawarma) were bought at commercial

stores in Israel. Human gastric fluid (HGF) was collected with permissiomn from a fasting woman (age 25) during regular gastric endoscopic tests, and kept at -80°C pending use simulated gastric fluid (SGF) was freshly prepared according to the U.S. Pharmacopoeia (9).

Hydroperoxides measurement in linoleic acid emulsions

Spectroscopic measurements. Hydroperoxides determined by means of the ferrous ion oxidation- xylenol orange (FOX2) method (10), including spectral analysis at 560 nm with $H_2O_2$ standard curve.

Catechin was dissolved in 10% ethanol in water, thus the ethanol concentration in the reaction tubes were incubated in triplicate in a shaking bath at 37°C for 180 min. Samples of 25 or 50 µl were taken from the tubes during the incubation and added to 475 or 950 µl, respectively, of FOX2 reagent. Before each experiment, old stock solution of linoleic acid was mixed with fresh solution in order to maintain an accurately consistent initial level of hydroperoxides.

I had been confirmed in preliminary experiments that the presence of metMb, Fe, AA, wine, or catechin themselves, at the concentrations used, did not interfere with the FOX2 assay.

Hydroperoxides measurement in turkey muscle tissue

The grilled turkey meat, in the form of small slices, was divided into portions and kept at -80°C peding use in the experiment. One part of this muscle tissue was ground with three parts of liquid for 1 min. in a lavoratory blender (Waring, New Hartford, CT, USA) and adjusted to pH 3.0. the liquid contained SGF with red wine, or ethanol solution or water as controls. The wine was diluted with 12% ethanol solution, so that the ethanol content (final concentration 6%) was equal in all of the treatments, except for the water control. The meat –liquid mixture of each treatment was divided among several tubes and incubated in a shaking bath at 37°C for 180 min. At five times points, the hydroperoxides in the samples were extracted by 10-fold dilution in methanol under slow stirring for 15 min, followed by paper filtering (cat. No. 1442, Whatman, England). One hundred microliter samples of the filtered solution were

subjected to the FOX2 assay, which included TTP reagent controls, in order to prevent potential interference from ferric ions and the red wine pigments.

Results

Grilled turkey meat, one part of this muscle tissue was ground with three parts of simulated gastric fluid for 30 sec in a laboratory blender and adjusted to pH 3.0.

The heated red turkey meat was found to contain about 180 μM hydroperoxides and malondialdehydes concentration 10-20 times higher than those in the fresh muscle.

In addition to control the heated red turkey muscle was ground in the presene of an Antacid changing the pH to 5.0 and with or without catechin to a concentration of 2.5 mM. The results show a rapid lipid peroxidation in the control samples and after a incubation of 180 min the level of the hydroperoxides rose to more than 1400 μM.

Lipid peroxidation of the sample contained antacid, which change the pH of the gastric fluid to 5.0 decrease lipid peroxidation and the accumulations of hydroperoxides.

However, the sample contained both Antacid and catechin not only inhibited lipid peroxidation, but also reversed the reaction and broke down hydroperoxides to zero concentration.

Discussion

Lipid peroxidation in red muscle tissue is potentially catalyzed by an iron-redox cycle formed by ferrous ions and ascorbic acid. Metmyoglobin, the red pigment could work in muscle tissue as a prooxidant or antioxidant (11, 12). Our data demonstrated that human stomach fluid, having low pH and dissolved oxygen following a meal, is a suitable medium for further lipid peroxidation. The acidic pH of the gastric fluid significantly amplified the peroxidation of lipids catalyzed by dietary endogenous catalysts, found in foods such "free" iron or hemeproteins. These results are in agreement with others which found that the consumption of hydroperoxides and hydrogen peroxide with "free" iron or metmyoglobin is stongly pH dependent (5).

Plant derived polyphenolic antioxidants such as red-wine not only prevented the build up of oxidized products, but also in association with heme-proteins, stimultated the hydroperoxides breakdown and inverted catalysis from pro-oxidation to antioxidation.

Several factors affect the displacement of electrons and hydrogen from the phenolic

hydroxyl group; they include additional OH or OR groups around benzoid ring and pH. High pH increase the rate of hydrogen displacement from polyphenolic compounds and therefore increase their antioxidant effects (13).

The introduction in the system of antacid and catechin inverted the reaction from prooxidation to antioxidation. Once the concentration of the hydroperoxides drop to zero, the system remains stable against pro-oxidative effects for long time (Figure 1). The synergistic effect of antacid on the activity of the catalyzers and antioxidant was achived because by increasing the pH the prooxidative effects drop and the catechin antioxidative activity rose two effects which work to increase the antioxidative tone of the system.

The antiulcerogenic and anti-oxidant effects of verious flavonoids have been frequently reported (6,7). More over, catechin was found to significantly inhibited the release of gastrin, somatin and histamine (7).

We believe that a combination between an antiacid and a polyphenol antioxidant such catechin, quercetin or other polyphenols could be used as a therapeotic digestive additive before meal to prevent and suppress gastric mucosa lesions in human.

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Appendix II

Examples

Example 1)

Synergistic composition of Antacids and Flavonoids to protect antioxidants' supplements (from becoming proxidants in the stomach acidity)

Abstract: Free radicals are produced continuously in cells as part of normal cellular function and Antioxidants are important to enable the cell metabolism continue under control and prevent free radical induced tissue damage by preventing the formation of radicals, scavenging them, or by promoting their decomposition.

Whereas epidemiological researches proved the correlation between the consumption of antioxidants and reduced risk for western diseases- CVD, Cancer, Diabetes, Inflammation, neurological conditions skin etc, intervention trials didn't prove significant contribution for their supplementation. Not only disappointing results but recent researches suggested that Antioxidants' supplement could increase the risk for CVD and Cancer. This lead to the suggestion that there is insufficient data from well-designed randomized trials to issue a general recommendation for people to take supplements of the antioxidant vitamins in order to prevent heart and cancer diseases ,thus eating

lots of fruits and vegetables seems the most prudent course at the moment.

The fact that the chemical and physiological states of the antioxidats/proxidants is affected by the internal and environmental conditions, the question raised is if it will be possible to protect the Antioxidants in a way that will preserve their function as antioxidants.

The Synergistic protection of the antioxidants , each protecting and helping others in self-regeneration, could explain the advantage of the complete fruits and vegetables over the single-antioxidant supplement in reducing the risks.

In light of the new research showing that the stomach acidity is a most sensitive environment for oxidation, the question regarding the possibility of Antacids providing a protection for antioxidants' supplements. Adding antacids, might reduce the rates of in-stomach oxidation, which otherwise could ended up in most of the antioxidants turned to become proxidants already in the stomach..

The present invention relates to the synergistic composition of Antacids with Antioxidants' supplements aiming for the increased their protection and effectiveness.

1a) Antioxidants function against Free Radicals:

Free radical production occurs continuously in all cells as part of normal cellular function. However; excess free radical production originating from endogenous or exogenous sources might play a role in many diseases.

Antioxidants are needed to prevent the formation, scavenging them, promoting their decomposition and oppose the actions of reactive oxygen and nitrogen species, which are generated in vivo and cause damage to DNA, lipids, proteins, and other biomolecules. Endogenous antioxidant defenses (superoxide dismutases, H2O2-removing enzymes, metal binding proteins) are inadequate to prevent damage completely, so diet-derived antioxidants are important in maintaining health. Many dietary compounds have been suggested to be important antioxidants: The evidence for a key role of vitamins E and C is strong, but that for carotenoids and related plant pigments is weaker. Interest is also growing in the role of plant phenolics, especially flavonoids. Some antioxidants can exert prooxidant effects in vitro, but their physiological relevance is uncertain (Young IS).

1b)Stomach Acidity facilitates Peroxidation: The acidic pH of gastric fluid amplified lipid peroxidation catalyzed by met myoglobin or iron ions. Met myoglobin catalyzed peroxidation of eatable oil, resulting in 8-fold increase of hydroperoxide concentration. The incubation of heated muscle tissue in simulated gastric fluid for 2 h enhanced hydroperoxides accumulation by 6-fold to 120..

Muscle foods contain large amounts of endogenous catalysts, such as "free" iron ions and met-myoglobin, which accelerate lipid peroxidation [13]. The cross reactions between lipid free radicals generated during lipid peroxidation and other food constituents dramatically alter the range of cytotoxic and atherogenic compounds produced including hydroperoxides, oxycholesterols, malondialdehyde, and hydroxy alkalans [14,15]. Hence Lipid hydroperoxides are not only formed in foods, but may also be generated during digestion, especially in the gastric fluid, which contains absorbed oxygen and has a low pH. These suggest that human gastric fluid may be an excellent medium for enhancing the oxidation of lipids and other dietary constituents (Kaner et al,2001).

1c)Combined Antacid and Antioxidative activities of polyphenoles

In a simulated acidic pH environment of the stomach, when the generation or breakdown of dietary hydroperoxides by the endogenous catalysts found in foods were measured, dietary polyphenols could invert the catalyzed reaction from pro-oxidation to antioxidation and consequently prevent the overall lipid peroxidation in the stomach. This might help to explain the health benefits of diets rich in polyphenolic antioxidants.

In the presence of catechin or red wine polyphenols, met myoglobin catalyzed the breakdown of hydroperoxides to zero, totally preventing lipid peroxidation and Beta-carotene co-oxidation.

Polyphenolic metabolites of plants, common in the human diet, are found in fruits, vegetables, and their products such as red wine, cider, and tea. They have been shown to act as strong antioxidants in various systems [ 16,17] and their multiple biological actions have been reviewed [18]. Many epidemiological studies have shown an inverse association between the consumption of fruit, vegetables, and their products in daily human diet, and the incidence of cardiovascular diseases and cancer [19,20].

EXAMPLE 2): Synergistic composition of Antacids & Antioxidants for protecting Vit E in Turkey Stomach & Meat.

Summary: Turkey meat is more susceptible to storage conditions and this has strong market and economic disadvantages. Research showed that Vit E , which is a known protector of meat, due to its Antioxidative protection, is much lower in turkey, which could explain the low storage resistance. Research showed that dietary Vit E is lost from feed to duodenum, namely along the passage through the stomach. Beyond the stomach acidity effect that might facilitate Vit E oxidation, many turkey growers use Acidifiers for improving growth rates and health. It is suggested that a combination of Antiacid and Antioxidants could protect Vit E along the stomach, enabeling it to reach the small intestine, absorbed and increase the Vit E content of the meat and thus increase storage preservation.

E)Turkey's vit. E levels is lower than chicken (Sklan D, 1982)

When Chickens and turkeys were fed basal diets to which tocopherol was added at levels of 10, 50 and 250 mg/kg for 28 days. Plasma and liver tocopherol levels were correlated with dietary tocopherol in both chickens and turkeys, but concentrations were 1.5- to 4.5-fold lower in turkeys. Disappearance (absorption + catabolism) of tocopherol between feed and lower ileum was 78-90% of the ingested vitamin, and no significant differences were found with dietary intake or between chickens and turkeys. Of the 3H-labeled material found in the duodenum, 24-40% by comprised mainly tocopheryl glucuronides. Turkeys excreted 2.5- to 7-fold more glucuronides than chickens, which explains partially lower plasma and tissue concentrations of tocopherol in turkeys.

When chicks and turkeys fed the same amount of tocopherol, Mecchi et al. (6) found that chicken carcass fat contained Fourfold or fivefold higher hepatic and breast muscles tocopherols in chickens.

Some 45-60% of tocopherol was found to have disappered between feed and duodenum althotlgh major absorption of other lipids has been shown to occur mainly in the duodenum and upper jejunum.

This disappearance is accounted for, in part, by the high levels of tocopheryl-quinon found in the duodenum. That might caused by oxidation of tocopherol prior to the small intestine (23). The major metabolite has been shown to be tocopherol quinone in the intestine, feces , lymph , tissues and plasma. This irrevirsible convertion represents a nutritional loss of tocopherol.

In chicks glucuronides comprised 5-10% of tocopherol intake, whereas in turkeys this ranged from 30-40%. This parallels the IO fold enhanced secretion of polar metabolites of cholecalciferol in turkeys as compared to chickens (19).

Hence, the lower tocopherol levels in turkey tissues are explained, partially, by greater production and excretion of tocopheryl glucuronides and oxidation to quinon.

E) Dietary Vitamin E in ... Oxidative Stability of Turkey Meat During Storage (J Kanner)

Thiobarbituric acid reactive substances (TBARS) values of the meat gradually increased as its storage duration increased from about 15 to 120 d.

The TBARS values of the meat up to about 30 d of storage were significantly lower due to the supplementation of the diet with vitamin E at a level of 28 mg/kg in one out of three experiments and at a level of 150 mg/kg in two out of two experiments. The protective effect of the higher level of vitamin E remained evident after about 108 d of storage. No interaction was observed between Fe and vitamin E treatments in their effect on TBARS values.

The results show that high levels of dietary Fe do not adversely affect the oxidative stability of thigh meat of turkey; however, dietary vitamin E, at a level of 150 mg/kg, consistently increased this stability.

A) Stomach acidity for Animal Health and Performance

Monogastric animals, such as swine and poultry, must keep a low gastric pH to maintain a healthy gut. This is one of the major factors governing the performance of monogastric animals and, thus, the economics of livestock production. Yet this balance often cannot be reached or maintained under various conditions when animals are young, or under sub-clinical stress

B) WHY TO ACIDIFY THE INTESTINE OF POULTRY?

Poultry diets usually have high alkalinity characteristics: i.e broiler and turkey formulations (very rich in protein and nitrogenous substances) or formulations for layers and breeders (that are characterised by a high contents of mineral and of calcium in particular). Such nutritional needs lead to a large use of vegetable protein and calcium carbonate meals that in feeds have a strong buffer function .

Acidifiers acids and their salts have long been used to preserve food, feedstuffs, and also used by poultry and swine producers to help maintain an animal's healthy intestinal environment and beneficial microbial balance.

C) WHY TO USE PROTECTED ACIDIFIERS?

- The production of pepsinogen and of hydrochloric acid inside proventriculus is higher than in mammals, with a continuous production flow.
- This implies that the acidification strategy shall have intestine as main target organ.

- We can obtain the reduction of pH in feed, in the first digestive tract and in the stomach, by using acidifiers in free form or as salt, even if the stomach does not need any help in this sense, as we can see in table 3. The acids coming out from the stomach are buffered by the biliary salts, loosing efficiency in modulating the intestinal pH, they would also be used as energy source in the first intestinal tract in case they are organic.

- Decrease of the number of germs inside the intestinal lumen
- Increase of saprophyte microflora to the detriment of the main pathogens
- Increase of the villi length and decrease of the intestine mucosa thickness following to reduction of the germs number in the intestinal lumen, with the result of improve both the feeds digestibility and the feed converstion rate.
- Strong anti-clostridia activity
- Increase of microflora that can produce organic acids (such as lactic, propionic and acetyc acid) that give an energetic support; they contribute to keep the optimal pH level and have an antagonist activity towards all Salmonella strains and other pathogen germs.
-

<u>POULTRY ACIDifiers - USE AND DOSAGE</u>

Poultry acid shall be carefully mixed at the dose of 60-100g per 100kg of feed as auxinic and as growth promoter.

In layers and breeders we advice a periodic use of it at the dose of 200g per 100kg of feed, for periods of 6 – 8 days a month or every other month.

EXAMPLES 3- B CAROTENE

Synergistic composition of Antacids and Antioxidants for Protection of B-carotene against Stomach oxidation

The clinical protection of Beta-Carotene

Beta-carotene and Cancer

Protection against cancer:Several studies have shown that beta-carotene may reduce the risk for prostate cancer. Also, epidemiological stydies showed that Beta-Carotene was inversely correlated with risk of lung Cancer .

Dietary intact Carotenoids

The associations between dietary ß-carotene, ß-carotene, lutein/zeaxanthin, lycopene, ß-cryptoxanthin, vitamin A, serum ß-carotene, and serum retinol and the lung cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention was studied in cohort of male smokers conducted in southwestern Finland between 1985 and 1993(*Am J Epidemiol* 2002; 156:536-547).

The failure of intervention studies:However, several intervention studies have not confirmed that beta-carotene protect against lung cancer: Alpha-tocopherol, Beta-carotene (ATBC) Cancer Prevention Study on the effect of supplementing male smokers from Finland (ages 50-69) with beta-carotene 20 mg (approximately 33,000 IU), vitamin E 50 mg (approximately 70 IU), both beta+carotene and vitamin E, or a placebo (an inactive pill) to determine if the supplementation would prevent lung cancer or other types of cancer. Beta-Carotene and Retinol Efficacy Trial (CARET in smokers or those exposed to asbestos was stopped early due to the ATBC study preliminary results showing no benefit and potential negative health impact from the beta-carotene and vitamin-A supplementation in this particular group of people.

Many scientists agree that there is significant research establishing a potential role for beta-carotene in prevention of certain types of cancer and other diseases. Although the reasons for the unexpected results of these two studies are unclear.

B1) Beta carotene oxidation under acidic conditions

Recent research (Kanner J, 2001) showed a dramatic increase in beta carotene oxidation under acidic conditions of the gastric simulated fluid. Here B carotene co-

oxidation was determined in order to identify free radical damage during lipid peroxidation in the same model system of acid gastric fluid.

The addition of metmyoglobin to the system catalyzed the bleaching of b carotene, demonstrating free radical damage to the target molecule. However, the addition of catechin to the same system containing metmyoglobin inhibited b carotene oxidation by 100%.

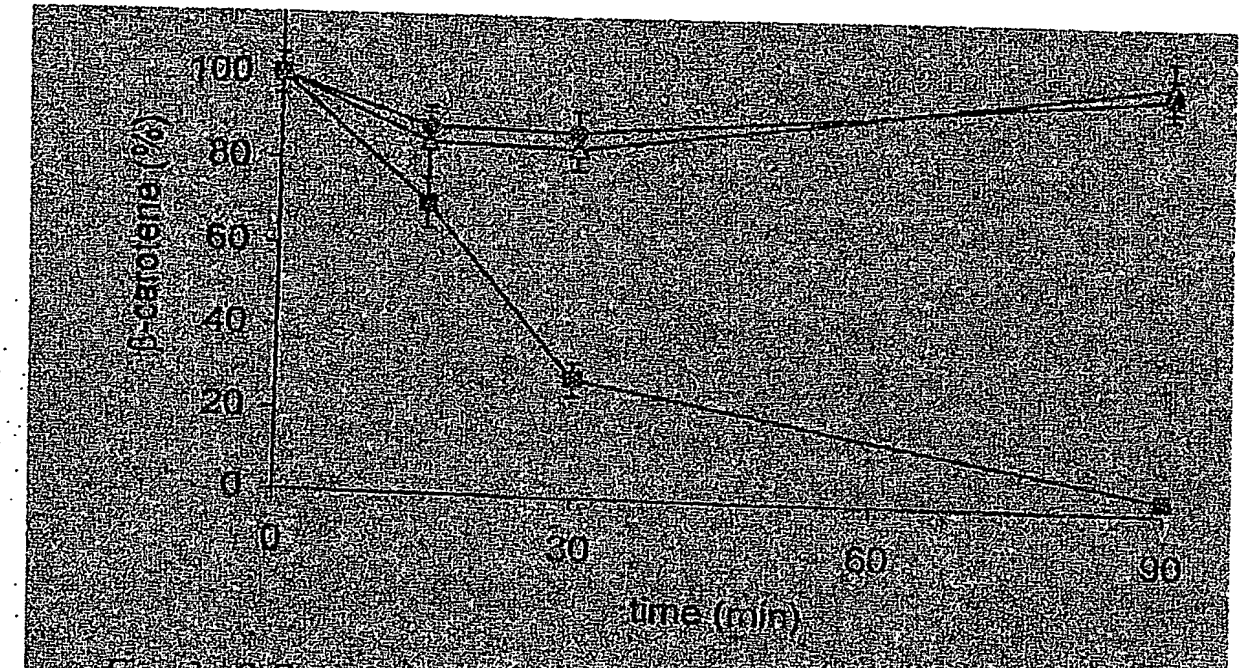


Fig. 3. β-Carotene co-oxidation in simulated gastric fluid (pH 2.0) containing linoleic acid, hydroperoxides, and catalysts during incubation at 37°C. (Δ) Control containing β-carotene, linoleic acid, and hydroperoxides; (■) in the presence of $Fe^{3+}$ (10 μM), AA (100 μM), and metMb (20 μM); (●) in the presence of $Fe^{3+}$ (10 μM), AA (100 μM), metMb (20 μM), and catechin (2.5 mM). Data are means ± SD ($n = 2$).

B2) Smoking might further facilitate intragastric oxidation

B2a) Cigarette smoking promotes atrophic gastritis in Helicobacter pylori-positive subjects.(Nakamura M, 2000)

Aging and smoking are known to promote atrophic gastritis (AG) and intestinal metaplasia (IM). An increased risk of severe AG/IM was statistically associated with

smoking (OR 9.31, OR 4.91,) and high TBA concentrations (OR 2.92). Thus cigarette use and high TBA (Total Bile Acids)concentrations may play a role in the progression of AG and IM in Hp-positive subjects.

B2d)Effect of cigarette smoking on gastropharyngeal and gastroesophageal reflux (Smit CF, 2001)

Cigarette smoking is known to affect adversely the defense mechanisms against reflux of acid gastric contents into the esophagus.

The percentage of time the pH was below 4 during the smoking period was significantly higher than during the nonsmoking period, at the proximal, the upper esophageal sphincter, distal and above the lower esophageal sphincter. These findings demonstrate that smoking increases gastropharyngeal and gastroesophageal reflux.

The synergistic effect

Beta-carotene and the other carotenoids are only one small component of a healthy diet or supplement program that may help preserve good health and prevent disease. There is much scientific support that a high intake of fruits and vegetables may prevent cancer, heart disease, and other degenerative diseases.

Research indicates that it may take consuming five to ten servings of fruits and vegetables every day to achieve these health benefits. Most Americans do not consume this level of fruit and vegetable intake and therefore may consider a blend of antioxidant supplements to help fill in the gaps.

B2E) Low Nutrition status of smokers

The nicotine in cigarettes causes damage to our body, but smokers also tend to have diets low in a number of essential nutrients. Records of more than 6700 adults showed a decreased intake of fruits and vegetables in smokers, causing low levels of antioxidants. The 1994-1995 National Diet and Nutrition Survey in mainland Britain also noted decreased levels of antioxidants, as well as lower folate intake in smokers. An analysis of 51 nutrition surveys from 15 countries examined 47,250 nonsmokers and 35,870 smokers. Smokers had an increased intake of calories, total fat, saturated fat, cholesterol and alcohol. They also had a decreased intake of fiber, beta-carotene, and vitamins C and E.

The bottom line is that beyond the nicotine and oxidative stress by the free radicals' formation,starting and critically amplyfied in the stomach acidity, the poor dietary intake surely increase the damage of sicarettes' smoking.

B3) Potential protection of antacid

Awereness to the stomach related risk of oxidation could help better protection of the beta-carotene, i.e. taking Tums & Flavonoids with Beta Carotene, preferabely together with synergistic composition of other antioxidants. This way the body could benefit more from the Antioxidavie characteristics of Beta-Carotene rather than getting it in the proxidtive status which could facilitate the damage rather than repairing it.

Example): Synergistic composition against Stomach ulcers in horses

High Incidence: Studies in England, Ireland, Hong Kong and the United States report that 80-90% of racehorses in training, 84% of yearlings and 51% of foals have stomach ulcers. In racehorses spelled for a month, the incidence of ulcers is around 50%. In horses trained out of the paddock and eating a fully steam-extruded concentrate, the incidence was 10%. Other research found that 50% of ponies on concentrates had ulcers, whereas ponies on hay diets did not.

*In foals, 30% of deaths between 1 and 4 months of age, are related to stomach ulcers. The period of highest risk for developing ulcers is from 2 days to 8 weeks after birth - especially in foals with diarrhoea.*

Two major causes of gastric ulceration: 1 )Reduced ability of the stomach to defend itself against gastric acid and digestive enzymes. Stress reduces normal protective mechanisms within the stomach. The major risk period is between 1 and 3 months of age - that is, before foals have begun eating sufficient solid food for saliva production to buffer stomach acid production. 2) Prolonged exposure of the stomach to high acid levels. High acid levels result from modern feeding practices. Both fasting and high grain diets predispose to gastric ulceration. Horses and ponies in stables and those on high raw grain diets have more ulcers than those at pasture or on hay diets.

Horses's stomach function and protection: Horse's stomach is made up of two different parts. The first type of epithelium encountered in the stomach is stratified squamous epithelium, after which a glandular epithelium is found. A distinct margin, called the margo plicatus, separates the two.

Hydrochloric acid (gastric acid) and pepsin, are produced in the glandular portion which also secretes factors that help to protect the stomach, i.e. a mucus-bicarbonate layer serves to protect the stomach lining both by preventing acid from physical contact with the stomach surface, and by buffering gastric acid at the level of the stomach lining.

This mucous-bicarbonate layer protects only the glandular portion of the stomach, and not the squamous portion. Other protective factors include prostaglandin E, which causes increased blood flow in the stomach lining, increased secretion of the mucus-bicarbonate layer, and also causes decreases in hydrochloric acid production.

Continuous acid secretion: Unlike humans, horses produce gastric acid continually regardless of whether they are eating regularly. The ph of gastric From feed several hours- 2.0 or less. Horses on free choice had ph=3.1 compared to 1.5 in the fasted horses.If horses do not eat, then their stomachs become more and more acidic because acid production cannot be turned off. The squamous portion of the stomach is at the greatest risk from increased acid production, because it does not benefit from all the protective factors that the glandular portion of the stomach enjoys.

Fast eating: Studies on pellets suggest acid secretion increases in response to pelleted feed, because pellets are eaten rapidly. Both yearling and adult horses consume pellets faster than they eat traditional grain diets.The amount of bicarbonate in saliva increases as saliva production increases and so the longer the horse takes to eat a feed,

Management, treatment and prevention: Treatment involves – 1. Acid-suppressive therapy using drugs to inhibit acid formation. Horses in work respond less favourably than those at rest. Acid-suppressive therapy is expensive. If a lower dose is used for economic reasons, healing may not occur in many horses and it will be more costly in the longer term. 2. Antacids are of benefit in alleviating clinical signs of poor appetite and mild colic, but they are relatively ineffective in healing gastric ulcers.( Jennifer H

Stewart Equine Veterinarian and Consultant Natritionist to The Australian Feed Co).

NSAIDS cause gastric ulceration in horses:Common NSAIDs include phenylbutazone ('bute') and flunixin meglumine (Banamine™). They act by interrupting the production of prostaglandins. One particular prostaglandin, called PgE2, plays an important role in preventing gastric ulceration. PgE2 does this by decreasing gastric acid production as well as by increasing blood flow to the gastric epithelium. The results are - the horse's stomach becomes more acidic, and this contributes to the development of gastric ulceration.

A designing Equine Antacid :For an antacid to work well in horses it must possess several properties: Easy administration, preferably by adding to the horse's feed. A small dose should neutralize a large amount of acid and it should coat and protect the mucosa from gastric acid irritation. In addition, antacids should be able to adsorb pepsin and other substances that can damage the mucosa. Finally, it should not affect fecal consistency and should create no harmful side effects.

Kentucky Equine Research has worked to develop an equine antacid that would satisfy the above criteria. Unfortunately, Horses became ataxic and displayed signs of tying-up following high MgO which is one of the common antacids used for humans. Aluminum based antacid raised concern regarding interference with phosphorus absorption, but it appears that aluminum-containing antacids can be safely fed to horses.

A patented product: Neigh-Lox comes in a palatable pelleted form that can be fed alone or mixed in feed. It contains a very fast acting antacid with 240 mequ/dose of acid neutralizing capacity. A four ounce (120 g) dose will neutralize about 6 hours of basal acid production.

The recommended dosage for adult performance horses is 4 ounces per meal with a maximum daily intake of 16 ounces. Neigh-Lox also contains a compound that serves as a coating agent to protect the gastric mucosa. This ingredient has an astringent and anti-inflammatory action and pepsin binding capacity.

Field success: Neigh-Lox has been field tested in hundreds of horses. Many horses that displayed signs of gastric irritation such as poor appetite, chronic colic, and sour

disposition have shown immediate improvement after receiving only a few doses of Neigh-Lox. Since there are no studies to show that Neigh-Lox heals ulcers, it is recommended only as adjunctive therapy to acid suppressive drugs in horses that have been positively diagnosed with gastric ulcers. Neigh-Lox's most important role, however, may be in preventing ulcers from occurring in the first place in horses and foals.

Neigh-Lox (Kentucky Equine Research, Inc.): "An equine antacid An aid in the reduction of excess gastric acid in horses and foals caused by high grain intakes".

NEIGH-LOX is a pelleted antacid designed specifically for horses. Horses produce stomach acid continuously throughout the day. When horses graze they normally secrete saliva constantly which buffers stomach acid. When horses are being ridden regularly, trained for shows or prepared for sales, they are usually kept in stalls much of the day. Under these conditions, the natural buffering mechanism is disrupted and acid indigestion often results. NEIGH-LOX is designed to restore normal stomach function.

INSTRUCTIONS: Feeding Directions: For growing horses 6 to 12 months of age, add 2 oz of NEIGH-LOX to each grain meal. For yearlings 12 to 24 months of age, add 4 oz of NEIGH-LOX to each grain meal.

For horses in training, add 4 oz of NEIGH-LOX to each grain meal.

INGREDIENTS:Ground wheat, steamrolled oats, dihydroxy-aluminum sodium carbonate (DASC), aluminum phosphate, soybean oil, dicalcium phosphate, and calcium carbonate.

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Claims:

1. A method of protecting an orally consumed or administered agent, said agent is oxidizable in a pH dependent manner, the method comprising co consuming or co administering with said agent at least one substance, said at least one substance for increasing the pH in the stomach.

2. A method of preventing oxidative damages associated with oral intake of an agent, said agent is oxidizable in a pH dependent manner, the method comprising co intaking with said agent at least one substance, said at least one substance for increasing the pH in the stomach.

3. A method of preventing food or medicine intake associated oxidants formation in the stomach, the method comprising, co intaking with the food or medicine at least one antioxidant and at least one substance for increasing the pH in the stomach.

4. A method of inhibiting co oxidation processes in the stomach, the method comprising co administering at least one antioxidant and at least one substance for increasing the pH in the stomach.

5. A method of alleviating or reliving heart burns and GERD symptoms, the method comprising co administering at least one antioxidant and at least one substance for increasing the pH in the stomach.

6. A pharmaceutical composition for oral intake comprising as a first active ingredient at least one antioxidant and as a second active ingredient at least one substance for increasing the pH in the stomach.